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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,886	05/15/2001	Barry Coller	A31386-A	1518

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 01/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,886	COLLER ET AL	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-11 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities: The first line of the specification should be updated to indicate that US application 09/090,757 is abandoned.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2 and 4-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to methods of administering monoclonal antibodies which bind to the integrins GPIIb/IIIa and $alpha_V$ $beta_3$ and act as antagonist of integrins GPIIb/IIIa and $alpha_V$ $beta_3$, wherein the antibody is 7E3 or a mouse/human chimera thereof, does not reasonably provide enablement for methods of administering any other antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method for inhibiting angiogenesis in a mammal comprising administering a monoclonal antibody or fragment which acts as an antagonist of the integrins GPIIb/IIIa and alpha$_V$ beta$_3$. The claims are broadly drawn to administering any antibody that is an antagonist of integrins GPIIb/IIIa and alpha$_V$ beta$_3$.

The specification has not demonstrated the reproducible production of antibodies which have properties identical to 7E3, nor of antibodies of other species origins which have the claimed properties, nor of antibodies that bind to the integrins GPIIb/IIIa and alpha$_V$ beta$_3$ and act as antagonist. The production of a hybridoma which secretes a monoclonal antibody having a particular set of specifically defined characteristics is an unpredictable event. Given that a single example of the isolation of an antibody having the claimed properties has been presented herein, it is not clear that the isolation of the 7E3 antibodies did not merely represent a fortuitous event. In view of the lack of predictability of isolating further antibodies which are functionally equivalent to 7E3 together with the lack of exemplary material presented herein, it appears that undue experimentation would be required of one of skill in the art to practice the invention as claimed using the technology of the specification alone.

The specification fails to set forth the reproducibility of the generically claimed monoclonal antibodies which bind to the integrins GPIIb/IIIa and alpha$_V$ beta$_3$ and act as antagonist to GPIIb/IIIa and alpha$_V$ beta$_3$, which are use in the claimed immunotherapy methods. In view of the unpredictability of producing antibodies having the claimed properties from among the 10^6- 10^{10} possible antibody variable region specificities encoded in the mammalian genome and in view of the lack of disclosure of the reproducibility of these antibodies, it does not appear that the antibodies required for the broadly claimed methods can be reproduced from the written disclosure alone.

It appears that the 7E3 antibody has unique properties of binding to both integrins GPIIb/IIIa and alpha$_V$ beta$_3$ and acting as antagonist is a property apparently unique to only this 7E3 antibody. The specification teaches the use of an antibody, AP3, that binds to both integrins GPIIb/IIIa and alpha$_V$ beta$_3$, however, it does not act as an antagonist (page 19 lines 3-4). Moreover, Reverter et al (J. Clin Invest. (1996) 98, pp 863-874, Invention Disclosure Statement # 8) state that "the combined inhibitory effect of 10E5 and LM609 did not equal that produced by 7E3 alone"(page 872, left column first full paragraph), further in indicating that 7E3 has the unique feature of inhibiting both integrins GPIIb/IIIa and alpha$_V$ beta$_3$ that one does not observe with either 10E5, LM609, or AP3.

Furthermore, although monoclonal antibodies are highly specific, the antibodies do possess a certain degree of cross reactivity (see column 4, lines 53-56 of US Patent 4,474,893 (Reading, C.L.), IDS #8). Further, Sevier et al (Clin Chem 1981; Vol 27 No 11:1797-1806, Ids #8) teach that if a hybridoma antibody binds to a common subunit, the antibody is not useful in a selective diagnostic procedure (see page 1798, right column). Besides the target of interest, there may be other structurally related substances present in the sample.

Additionally, as evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of affinity would be necessary for the antibodies of the claimed method of inhibiting angiogenesis so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

The specification provides inadequate direction for the method of inhibiting angiogenesis in a mammal using any antibody that is an antagonist of both integrins GPIIb/IIIa and alpha$_V$ beta$_3$, as broadly defined by the claims. Further, the specification does not teach any other antibody that has the properties of the 7E3 antibody. Taken in view of the teachings of Reverter et al, Seaver, Sevier et al and Reading cited in support of the unpredictability of the art, undue experimentation would be required to make and use the invention commensurate with the scope of the broadly written claims. Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation.

Therefore, reasonable doubt exists as to whether the isolation of the monoclonal antibodies may have been fortuitous and not reproducible without undue experimentation. Filing of evidence of the reproducibility of the claimed monoclonal antibodies without undue experimentation coupled with evidence of the public

availability of the starting materials necessary to produce the claimed antibodies is accordingly required.

Alternatively, amending the independent claims to recite "wherein the antibody or antigen binding fragment thereof is 7E3" may be sufficient to obviate this rejection.

Deposit of Biological Materials

5. Claim 3 would be rejected under 35 U.S.C. § 112, first paragraph, however, the hybridoma recited as ATCC HB 8832 is available commercially from the ATCC.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al (Blood, Vol. 89 (1997), pp 4078-4084, Information Disclosure Statement #8) and Coller et al (Haemostasis (1996) 26, pp 285-293, IDS #8) further in view of Friedlander et al (Proc Natl. Acad. Sci. U.S.A. 93 (1996), pp 9764-9769, IDS #8), and Brooks et al (US 5, 753, 230, Filed Mar. 18, 1994, IDS #8).

The claims are drawn to a method for inhibiting angiogenesis in a mammal comprising administering a monoclonal antibody or fragment which acts as an antagonist of the integrins GPIIb/IIIa and $alpha_V$ $beta_3$ wherein the antibody is 7E3 or a mouse/human chimeric thereof and has the characteristics recited in claim 4 and the antibody is administered intravenously, in an amount of about 0.25 mg/kg followed by infusion of 0.125 mk/kg/min of antibody, wherein the mammal is a primate or dog or cat or human, and method treats inflammatory disease from group consisting of rheumatoid arthritis, macular degeneration, psoriasis, diabetic retinopathy.

Taylor et al teach the use of 7E3 $f(ab')_2$ as well as the chimeric mouse/human c7E3 antibodies for the protection against microangiopathic hemolytic anemia and microvasular thrombotic renal failure in Baboons. Taylor et al also teach administering the antibody intravenously, in a 0.25 mg/kg amount, or in the amount of about 0.25 mg/kg body weight followed by infusion of 0.25 to 0.35 mg/kg over 6 hours (page 4079) to a baboon. Taylor et al does not specifically teach the use of 7E3 in angiogenesis or

treatment of an inflammatory disease such as macular degeneration and that 7E3 are antagonist of both integrins GPIIb/IIIa and alpha$_V$ beta$_3$. These discrepancies are made up by the teachings of Friedlander et al , Brooks et al, and Coller et al.

Friedlander et al teach the involvement of integrin alpha$_V$ beta$_3$ in angiogenesis, more specific, macular degeneration in humans (see abstract) and the use of a conformation specific antibody to alpha$_V$ beta$_3$ (page 9764, Material and Methods). Friedlander et al also teach the use of "integrin antagonists as anti-angiogenic agents represents a potentially powerful therapeutic approach: the mechanism of action is well characterized, they appear to be highly specific for actively proliferating vascular endothelial cells with no significant effect on mature blood vessels and they interfere with angiogenesis at the final common pathway, regardless of the specific angiogenic stimulus". (page 9769 last paragraph).

Brooks et al teach that angiogenesis is an important process in not only neonatal growth but in wound healing and in pathogenesis of a large variety of clinical diseases including tissue inflammation, arthritis, tumor growth, diabetic retinopathy, macular degeneration by neovascularization of the retina, and the like. (Column 2 lines 5-10). Brooks et al also teach "that angiogenesis in tissues requires integrin alpha$_V$ beta$_3$, and that inhibitors of alpha$_V$ beta$_3$ can inhibit angiogenesis." (Column 3, lines 2-4).

Coller et al teach that "all forms of 7E3 inhibit the function of the alpha$_V$ beta$_3$ vitronectin receptor in addition to inhibiting GPIIb/IIIa" (page 287 top third of page).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the 7E3 antibody, that are antagonist of integrins GPIIb/IIIa and alpha$_V$ beta$_3$ as taught by Coller et al, in methods of intravenous administration at the amounts taught explicitly by Taylor et al for

inhibiting angiogenesis/inflammatory diseases in a human as taught by Friedlander et al and Brooks et al.

One of ordinary skill in the art would have been motivated to used the 7E3 and c7E3 antibody that are antagonist of integrins GPIIb/IIIa and alpha$_V$ beta$_3$ in methods of intravenous administration at the amounts taught explicitly by Taylor et al for inhibiting angiogenesis/inflammatory diseases in a human such as macular degeneration as taught by Friedlander et al and Brooks et al because Brooks et al teach "that angiogenesis in tissues requires integrin alpha$_V$ beta$_3$, and that inhibitors of alpha$_V$ beta$_3$ can inhibit angiogenesis." and because Coller et al teach that all forms of 7E3 inhibit the function of integrins GPIIb/IIIa and alpha$_V$ beta$_3$ and because Friedlander et al teach involvement of alpha$_V$ beta$_3$ in angiogenesis and macular degeneration.

Moreover, one of ordinary skill in the art would have had a reasonable expectation of success using the 7E3 antibody that are antagonist of integrins GPIIb/IIIa and alpha$_V$ beta$_3$ in methods of intravenous administration at the amounts taught explicitly by Taylor et al for inhibiting angiogenesis/inflammatory diseases in a human as taught by Friedlander et al and Brooks et al because Brooks et al teach the use of an antibody which inhibits the alpha$_V$ beta$_3$ receptor and inhibits angiogenesis/inflammatory diseases. In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Taylor et al had success in using the 7E3 antibody for platelet inhibition in a Baboon model and because Taylor et al used the c7E3 antibody, which is already humanized. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success because Friedlander et al teaches "integrin antagonists as anti-angiogenic agents represents a potentially powerful therapeutic approach: the mechanism of action is well characterized, they appear to be highly specific for actively proliferating vascular endothelial cells with no

significant effect on mature blood vessels and they interfere with angiogenesis at the final common pathway, regardless of the specific angiogenic stimulus" .

Although claim 4 recites specific characteristics of the antibody, it would be obvious that the 7E3 antibody have the claimed properties.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879